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Abstract: Background: This large-scale cluster-randomised controlled trial (cRCT) evaluated use of facemasks against laboratory-confirmed viral respiratory tract infections (vRTIs) and clinical respiratory infection (CRI) because previous studies have been inconclusive.

Methods: An open label cRCT, conducted in Makkah compared the offer and use of 50 surgical facemasks worn over five days versus no facemasks among pilgrims. Cluster-randomisation was by accommodation tents stratified by country and gender. Tents were allocated to groups by coin-tossing. Neither participants nor recruiting investigators could be blinded to the intervention. Facemask use and respiratory symptoms were recorded daily and nasal/pharyngeal swabs were collected from symptomatic participants for detection of respiratory viruses. Clinical and laboratory data were analysed for facemask efficacy against laboratory-confirmed vRTIs and CRI. The trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12613001018707.

Findings: From October 13 to 17 in 2013, October 2 to 6 in 2014, and September 22 to 26 in 2015, 7,687 adult participants from 318 tents were randomised to facemasks or no facemasks; 3,864 participants from 149 tents were assigned to the Facemask group and 3,823 participants from 169 tents to the Control group. In the Facemask arm, respectively 27% and 51% participants used facemasks daily and intermittently, 22% did not; in the Control arm, respectively 15% and 38% participants used facemasks daily and intermittently, 47% did not. Respiratory viruses were detected in 277 of 650 (43%) nasal/pharyngeal swabs from symptomatic pilgrims. In

intention-to-treat analysis, facemask use was neither effective against laboratory-confirmed vRTIs (OR 1.35, 95% CI 0.88-2.07) nor against CRI (OR 1.1, 95% CI 0.88-1.39), not even in per-protocol analysis (OR 1.2, 95% CI 0.87-1.69; OR 1.3, 95% CI 0.99-1.83).

Interpretation: Facemask use does not prevent clinical or laboratory-confirmed viral respiratory infections among Hajj pilgrims.

Funding: Qatar National Research Fund (number: NPRP 6-1505-3-358).

Facemask versus no facemask in preventing viral respiratory infections during Hajj: a cluster randomised open label trial

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Summary

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Methods An open label cRCT, conducted in Makkah compared the offer and use of 50 surgical facemasks worn over five days versus no facemasks among pilgrims. Cluster-randomisation was by accommodation tents stratified by country and gender. Tents were allocated to groups by coin-tossing. Neither participants nor recruiting investigators could be blinded to the intervention. Facemask use and respiratory symptoms were recorded daily and nasal/pharyngeal swabs were collected from symptomatic participants for detection of respiratory viruses. Clinical and laboratory data were analysed for facemask efficacy against laboratory-confirmed vRTIs and CRI. The trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12613001018707.

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Introduction

Viral respiratory tract infections (vRTIs) are a major public health burden, causing serious disease especially in vulnerable populations. Influenza-associated lower respiratory tract disease alone causes over 54 million infections per year, with 8 million cases of severe illness, and 145,000 deaths across all age groups.[1] Ever-increasing and faster international travel intensifies the transmission of influenza, especially in the setting of mass gatherings (MGs) such as Hajj pilgrimage in Makkah.[2] Non-pharmacological interventions such as facemasks, hand hygiene, social distancing, quarantine and institution closure may complement pharmacological measures like vaccination and antiviral use in the prevention and control of influenza and other vRTIs.[3]

While there is clinical and experimental evidence that surgical masks and respirators reduce virus transmission from infected patients, randomised controlled trials (RCTs) examining the effectiveness of facemasks in household, community or healthcare settings have been either conflicting or inconclusive.[4-10] While none of these studies found facemask use to significantly prevent clinical respiratory infections (CRI), one study did find protective efficacy of intermittent use of facemask against laboratory-confirmed influenza among households in a per-protocol analysis.[8]

Systematic reviews of RCTs conducted in community or healthcare settings show that wearing facemasks is protective against influenza-like illness (ILI), but not against laboratory-confirmed vRTI. The discrpenacy is thought to be due to inadequate sample size.[11-13]

Therefore we designed a large cluster-randomised controlled trial (cRCT) over three years among Hajj pilgrims to evaluate the efficacy of facemasks against laboratory-confirmed vRTIs.[13]

Methods

Study design

This was an open label cRCT conducted during Hajj in Mina, Greater Makkah, Saudi Arabia among pilgrims from Saudi Arabia, Australia and Qatar over three Hajj seasons, 2013–2015. Mina is an uninhabited valley at the outskirts of Makkah and has about 30,000 tents to accommodate pilgrims for up to five days as part of Hajj rituals. Generally, 50–150 pilgrims occupy each large tent, allocated by gender and country of origin, but tents with a much smaller number also exist. Pilgrims in each tent sleep close to each other, head-to-head, have meals and perform rites together hence are considered a cluster.

Ethical approval for this study was obtained in Saudi Arabia from the Institutional Review Board of King Abdullah Medical City (KAMC), Makkah, (IRB Ref. No.: 15-205), in Australia from the Hunter New England Human Research Ethics Committee (HNEHREC Reference No: 13/07/17/3.04), and in Qatar from the Joint Institutional Review Board of Hamad Medical Corporation/Weill Cornell Medical College (Ref: 13-00039).

A pilot RCT was conducted in Hajj season 2011 among Australian Hajj pilgrims to examine the feasibility of such a study and inform power calculations.[14] Subsequently the trial protocol was devised and published.[15]

Participants

Hajj pilgrims aged ≥18 years from participating countries staying in their allocated tents and able to provide signed informed consent were included. Participants aged <18 years or who had a known contraindication to mask use, had participated in another RCT investigating a medical intervention, or refused or were unable to sign the consent form were excluded.

Randomisation and masking

The Hajj tour group leaders for 346 tents, occupied by pilgrims from Saudi Arabia, Qatar and Australia, were asked before Hajj to facilitate the study and 318 agreed. The randomisation unit of this trial was the accommodation tent stratified by country and gender. Although as per protocol computer-generated random number by an offsite research coordinator was planned,

this was impractical in the field so that coin-tossing by an individual who was not a member of the research team (eg, a fellow pilgrim who was not a participant in the trial, a tour operator or a medical volunteer at Hajj who was not a stdy team member) was used to allocate an intervention. As the intervention of wearing a facemask was visible to participants and investigators, the trial could not be blinded, laboratory staff could be, and were blinded to the intervention.

Trained research team members approached adult pilgrims aged 18 years or older in their assigned tents and explained the study in detail on the first day of Hajj (October 13th in 2013, October 2nd in 2014 and September 22nd in 2015). Each research team member was assigned to about 15 participants from the first day of Hajj. The researchers gave pilgrims an information sheet and answered their queries. Pilgrims who agreed to participate in the study and signed an informed consent were included, asked to complete a baseline questionnaire and provided with a health diary in their preferred language (Arabic or English) to complete daily during the trial. Each participant was identified with a unique barcode number for use on their consent form, baseline questionnaire, health diary and any clinical specimens taken. A post-Hajj diary for an additional three days was attempted but because the return rate was negligible, this information was not considered for analysis.

The consent form and the baseline questionnaire were collected on the first day, but participants retained diaries for completion over the next four days of Hajj rituals while they were actively followed (Figure 1).

Procedures

Each participant in the Facemask group was provided with 50 surgical facemasks (3M^{TM} Standard Tie-On surgical mask, Cat No: 1816) in addition to verbal and printed instructions about appropriate facemask usage. Pilgrims in the Control group were not provided with facemasks and instructions, but could use their own masks if they chose to do so. All pilgrims

in both study arms were asked to record their facemask usage (including number of masks used and hours worn each study day) in their health diary daily for five consecutive days. For the analysis, pilgrims who used at least one facemask each day during Hajj were considered to have used a facemask during that day.

Outcomes

The primary objectives were to assess the role of facemasks in preventing the acquisition of laboratory-confirmed vRTIs and symptomatic respiratory infection. Thus the first primary endpoint was the efficacy of facemasks against laboratory-confirmed vRTIs, and the second primary endpoint was the efficacy of facemasks in CRIs among participants.

The research team actively searched for participants who developed respiratory or systemic symptoms on any day of the study, and asked them to record these symptoms into their health diary. They collected a nasal/pharyngeal swab from participants who developed subjective fever plus one respiratory symptom, or two or more respiratory symptoms without fever.

A total of 464 volunteer researchers were trained by the principal investigators before the study period. Training activities included how to approach pilgrims, trial processes, data collection, follow-ups, and sample collection and storage. Study team members were oriented to good clinical practice guidance for the conduct of clinical trials by the International Conference on Harmonisation.

From pilgrims with symptoms suggestive of respiratory infection a researcher collected a nasal or pharyngeal swab (FLOQSwabs™; COPAN Diagnostics Inc., Murrieta, CA) and placed it into UTM™ (COPAN) viral transport media. Symptomatic pilgrims were given generic medications for fever and pain, usually paracetamol.

Swabs labelled with the participant's unique barcode number were stored in an icebox at -20°C, before being re-stored by day's end in a –80°C freezer at the laboratory of the Hajj Research Center at Umm Al-Qura University, Makkah. After Hajj, these swabs were shipped

in refrigerated or cold containers to the Centre for Infectious Disease and Microbiology Laboratory Services, Westmead Hospital, NSW, Australia. There, nucleic acid was extracted with the Qiagen bioROBOT EZ instrument (Qiagen, Valencia, CA), and amplification was performed using the Roche LC 480 (Roche Diagnostics GmbH, Mannheim, Germany) instrument. Respiratory viruses were detected using a real-time, multiplex polymerase chain reaction (PCR) assay targeting human coronaviruses (OC43, 229E and NL63), influenza A and B viruses, respiratory syncytial virus (RSV), parainfluenza viruses 1–3, human metapneumovirus, rhinovirus, enterovirus and adenovirus. Middle East respiratory syndrome coronavirus (MERS-CoV) assay targeting the upstream region of the E gene (upE) was also performed.

Statistical analysis

Data from baseline questionnaires and health diaries were entered by trained research staff into customised web-based forms (WUFOO®, https://www.wufoo.com), and extracted into Excel sheets. Data checking against paper records was undertaken by four dedicated researchers (MA, OB, A-MB, MT).

Statistical analysis was performed using the SPSS Statistics® v25 (IBM, Chicago, IL, USA) and checked by a statistician using SAS V.9.3.

Assuming that the prevalence of symptomatic vRTIs is 30% in controls and the prevalence of laboratory-confirmed vRTIs in controls is approximately 12%, the intervention would be considered clinically worthwhile if it reduced the prevalence of syndromic or laboratory-confirmed vRTIs by 50%.

Assuming a moderate intra-cluster correlation of 0·1 and a mean of 75 participants per cluster (tent), and inflating the sample by a factor of 8·4 to account for clustering, the sample size required for a cRCT to detect a reduction from 12% to 6% with 80% power at 5% significance is 2,976 per arm. An additional inflation factor of 1·18 was included to allow for

up to 15% loss to follow-up or incomplete outcome data. This results in a sample size of approximately 3,500 participants per treatment arm, making a total of 7,000.

A descriptive analysis to compare the characteristics of participants in the two arms (Facemask and Control, both at tent level and at individual participant level, as appropriate) was performed. Categorical variables were described using frequencies and percentages and were compared, where appropriate, by using the Chi-squared test. Continuous data described using the mean and standard deviation, and were compared by the Student's t-test. The number or proportion of participants with missing data were reported for all variables, but comparisons between groups only included known values, except where otherwise specified. P values (p) and 95% confidence intervals (CIs) were presented without adjustment.

The first and second primary endpoints were analysed by intention-to-treat (ITT) analysis and participants were analysed according to their randomised treatment group regardless of treatment actually received. Outcomes were analysed using a generalised estimating equation (GEE) statistical model that accounted for the binary distribution of the data and the correlation between participants in the same tent, assuming an exchangeable correlation structure.

Exploratory multivariable analyses examined the effect of randomised treatment on outcomes in models adjusted for demographic factors, facemask usage and compliance with treatment. Subgroup analyses were conducted to compare the effect of treatment between groups of participants: male versus female, those with known risk factors versus those without risk factors or risk status unknown for vRTIs, vaccinated against influenza versus unvaccinated, smoker versus non-smoker, compliance with daily facemask use versus non-compliance, and by pilgrim's country of origin.

Subgroup analyses used the same statistical model as the primary outcomes and included an interaction term between randomised treatment and subgroup. If the p value for the interaction term was <0·05, the effect of treatment was described separately within each subgroup. Primary analysis included all participants who reported symptoms at any time during the study period. Eighteen participants who failed to report symptoms were excluded, but those (n=675) who reported symptoms only at baseline (ie, on day 1) were included. A per protocol analysis was undertaken amongst participants who were compliant with instructions at randomisation and reported symptoms daily after the baseline time point. An analysis was performed on participants who were symptom-free at baseline and who completed symptom reports at least once after baseline (ie, on day 1).

For the primary analysis, pilgrims who did not report symptoms daily were assumed to have no change in their symptoms compared to the most recent reporting day. Those who reported no symptoms on any study day were assumed to have never developed symptoms while those who reported symptoms on any day were considered symptomatic.

Role of the funding source

This study was supported by a National Priorities Research Program grant (NPRP 6-1505-3-358) from the Qatar National Research Fund (a member of Qatar Foundation). The funding body had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 318 tents that housed 11,227 pilgrims were recruited in both study arms over three Hajj seasons (13–17 October in 2013, 2–6 October in 2014 and 22–26 September in 2015) . The number of occupants in each tent varied according to the size of the tent, ranging from 6

to 150 pilgrims per tent. The total number of participants across all study years was 7,687 with an average participation rate of 69% (7,687/11,227) (ranged from 10% to 100% per tent). Of the total 7,687 participants, 3,864 from 149 tents were assigned to Facemask and 3,823 from 169 tents were assigned to Control group. Their age ranged from 18 to 95 years (median 34, mean 37, standard deviation [SD] 12 years), with 54% female, 6,998 (91%) were from Saudi Arabia and Qatar, and the rest were from Australia. A large proportion of pilgrims 58% (4,428/7,687) were recruited in the third year, 2015. The baseline characteristics are shown in Table 1.

Overall facemask use was low, even in the Facemask tents, with only 25% of participants using facemasks daily. Conversely, in the Control tents 14% participants used facemasks daily (Table 2). More participants in the Facemask group had used a facemask before the actual Hajj compared to those assigned in the Control group (28% versus 25%, p=0·0008) (Table 1). Over the study years, the use of facemasks in both groups combined decreased from 26% in 2013 to 22% in 2014 and 19% in 2015 (p<0·0001). Slightly more pilgrims in the Facemask group than in the Control group reported frequent hand washing during Hajj, including their ritual ablutions (69% versus 66%, p=0·009) (Table 2).

The proportion of pilgrims who participated in the study and used facemasks ranged between 0% and 50% per tent and that of pilgrims who reported developing CRI in each tent ranged between 0% and 46%. Linear regression showed no association between facemask use and CRI prevalence in individual tents (slope y=0·04, 95% CI–0·03 to 0·11; p=0·25) (Figure 2).

The most common side effects of using facemask were difficulty in breathing (26%) and discomfort (22%); a small minority (3%) reported feeling hot, sweating, a bad smell, or blurred vision with eyeglasses (Figure 3).

A total of 650 nasal/pharyngeal swabs were collected from symptomatic pilgrims in both groups. Overall, one or more respiratory viruses were detected in 277 (43%) of samples

tested. The most prevalent viruses were rhinovirus (35%), influenza, including A/H1N1 and A/H3N2 (5%), enterovirus (2%), and 2% had dual infections (Table 3).

In the ITT analysis, allocation to facemask use was not associated with reduced laboratory-confirmed vRTIs (odds ratio [OR] 1·35, 95% CI 0·88 to 2·07; p=0·18) or CRI (OR 1·10, 95% CI 0·88 to 1·39; p=0·40).

In subgroup analysis, there was evidence of a difference in the effect of the intervention between pilgrims who did and did not receive the influenza vaccine (interaction p=0·004). For vaccinated participants, there was no difference between the Facemask and Control groups in developing CRI, but in non-vaccinated participants there was a higher rate of CRI in the Facemask group (13% versus 10%, OR 1·4, 95% CI 1·0 to 2·0; p=0·03). Moreover, females in the Facemask group acquired more laboratory-confirmed vRTIs than females in the Control group (44% versus 29%, OR 1·9, 95% CI 1·2 to 3·0; p=0·004) (Table 4).

In a per-protocol analysis (including only participants allocated to the Facemask group who used facemasks daily, and participants allocated to the Control group who never used any facemasks) there was no benefit of facemask in preventing laboratory-confirmed vRTIs (OR= 1·21, 95% CI 0·87 to 1·69; p=0·26) or CRI (OR 1·34, 95% CI 0·99 to 1·83; p=0·06) (Tables 5 and 6).

Discussion

This cRCT showed that those randomised to facemask use had no apparent benefit against laboratory-confirmed or clinical vRTIs. These findings are similar to that of other smaller RCTs which examined the role of facemasks against clinical or laboratory-confirmed vRTIs in various settings that found no evidence of facemask benefit against clinical or proven respiratory infections.[6,7,9] Systematic reviews of available studies failed to demonstrate significant efficacy of facemasks against clinical or laboratory-confirmed vRTIs.[12,13,16,17] The large sample size in our cRCT enabled the comparison of a much larger number of clinical

infections (Facemask: Control= 354: 322) and many more laboratory-confirmed infections (Facemask: Control = 96: 60) with higher power than the other RCTs combined. A systematic review of 13 studies conducted at Hajj showed a significant protective effect of facemasks against all respiratory infections at Hajj (relative risk [RR] 0·89, 95% CI: 0·84–0·94; p<0·01) but individually only four studies demonstrated a significant effect of facemask against CRI, only two studies provided data on laboratory-confirmed infection and no individual study showed a significant effect.[18]

Facemask use may have been harmful among some participants such as those who were not vaccinated against influenza, and women. Unvaccinated pilgrims in the Facemask group had a higher rate of CRI than their counterpart in the Control group (13% versus 10%, p=0·03) which suggests vulnerability of unvaccinated pigrims to ILI. A previous study demonstrated that prevalence of ILI among Hajj pilgrims was inversely proportional to their influenza vaccination uptake,[19] and meta-analysis of data from six observational studies suggested influenza vaccine to be significantly protective against laboratory-confirmed influenza among Hajj pilgrims (RR 0·56; 95% CI 0·41–0·75).[20] More symptom development among facemask users have been reported in at least one other study in Hajj setting where 20·7% pilgrims who used a facemask reported fever compared with 15·6% who did not (p<0·01).[21]

It is unclear why females in the Facemask group were at higher risk of acquiring laboratory-confirmed vRTIs than in the Control group (44% versus 29%; p=0·004). This could be related to Saudi women's preference for using facecover over a facemask. Over 70% female pilgrims use a face veil during Hajj: one fifth of them use both face veil and mask. Compared with users at all times in public, women who use a facecover only occasionally (43·2%) or never (44·2%) tended to have higher rates of CRI.[22]Although we did not assess efacecover use by female pilgrims in our study, given that most pilgrims used facemasks only occasionally, the

higher rate of vRTIs among women might be due to intermittent use of facecover, though there could be other factors that remain unexplored at this stage or possibly a type 1 error. Lack of facemask effectiveness could be attributed to poor facemask use among participants (only 27% used daily and 51% used intermittently in the Facemask group), and the substantial proportion of participants in the Control tents who used facemasks, possibly reducing the ability of the study to detect differences in infection rates between the two arms.

Reported compliance in facemask use during MG settings varies widely. For instance, at Hajj the uptake of facemask use generally varies between 24% and 64%, while rarely it can be as low as 0·02% to as high as 93%.[18]A high rate of facemask use (80%) was observed among French Hajj pilgrims during the 2009 influenza pandemic year,[23] compared to about 54% in a non-pandemic year.[24] Pilgrims from Southeast Asia (eg, Malaysians) are more used to using facemasks during Hajj.[25] The lower uptake of facemasks among participants in our cRCT is similar to the poor uptake among Saudi Arabian (35–57%) and Australian pilgrims (53–57%) observed in previous surveys.[18] Although 78% in the Facemask group used facemasks, only a minority used them regularly (27%). The most common reasons for non-compliance, difficulty in breathing and feeling of discomfort (Figure 3), found also in previous surveys among Hajj pilgrims,[18] limited the use of facemasks in this cRCT.

In addition to poor compliance, poor facial fit might explain inadequate protection against vRTIs. In the present study surgical facemasks were used and our results may not be applicable to the use of N95 respirators, as these, if properly fitted, provide superior protection against CRI due to improved face-seal. However, N95 respirators are too expensive for public use, may be difficult to put on and uncomfortable to wear, and their inappropriate use might lead to accidental contamination, increasing the risk of acquiring vRTIs.[26,27]

The detection rate of respiratory viruses (43%) in our trial was higher than that reported in other studies (4–15%),[28] possibly due to the active case ascertainment strategy employed,

including close follow-up of the symptomatic participants. However, the distribution of the viruses was similar to that in other studies: ie, predominance of rhinovirus, followed by influenza, enterovirus, parainfluenza virus, coronavirus, adenovirus, RSV and others.[28] The prevalence of rhinovirus ranged from 5·9–48·8%, and the proportional contribution of influenza viruses ranged from 4·5–13·9%, with influenza A being the most predominant in most studies.[28]

No MERS-CoV was detected among the studied participants. Since the emergence of MERS-CoV in Saudi Arabia in 2013, transmission of this virus from Hajj has been feared to cause a global outbreak. Because of this threat, multiple surveillance studies among >10,000 pilgrims from various countries have been undertaken but have identified no Hajj-related case.[2]

To our knowledge this is the largest study on facemask efficacy against vRTIs. It was conducted in a unique MG setting where the transmission of vRTIs is known to be high. Nevertheless it does have the following limitations. Participants were followed up directly for only four days. Longer follow-up was attempted through post-Hajj surveillance, but the low compliance precuded any meaningful analysis. Pilgrims moving from place to place to accomplish Hajj rites made it difficult for researchers to follow them as well as was aimed. Many pilgrims randomised to the Control group used facemasks, contrary to the research protocol, but it would have been unethical to contradict Saudi Ministry of Health (MoH)'s official advice of facemask use while MERS-CoV was circulating in Saudi Arabia during our study period. A similar ethical issue applied in 2014 when fear of Ebolavirus disease prompted the World Health Organization (WHO) recommendation of facemask respiratory protection.[29] Suboptimal facemask use is the reality at population level but means that endpoints measured in our study do not represent the true effect of facemask. Our trial does indicate, however, that as a public health intervention, facemask use is not practicable. While our study protocol required a sample to be collected in participants with ILI, sampling was

performed in some who did not meet the ILI definition whilst others were not swabbed when symptomatic. Though cRCTdesign, not all occupants in the selected tents participated. On average 69% of tent occupants participated in the trial, ranging widely from 10% to 100%, with possible dilution of the effect of facemask intervention. The trial was conducted over three years,with uneven recruitment over the years, and most participants (58%) recruited in the final year (2015). The rate of CRI over study years was 15·5% in 2013, 8·3% in 2014, and 10·7% in 2015, reflecting the known seasonal variabilityof respiratory viruses, which may have affected the outcome of our study. Nine percent of participants in each study arm failed to return their diaries or report symptoms, and a similar proportion in each group were excluded for being symptomatic on the first trial day. Also, despite randomisation of tents, the individual participants in the groups differed in other aspects eg, gender, and use of facemask before enrolment (Tables 1 and 4). This could have resulted from uneven tent sizes and participation rates. Participating tents varied between the study arms (Facemask: Control =149: 169) because some tents, although designated as separate units, were later found to be parts of a larger tent. This was more common when several small tour groups were managed under a large tour operator and communal activities (eg, meals, congregational prayers, sermons) were combined in one large tent.

Over 80% of participants in our trial practised frequent hand washing, and the compliance was higher in the Facemask tents compared to the Control tents (84% versus 82%, p=0·03). This high rate of hand hygiene is consistent with findings from other observational studies involving Hajj pilgrims. In previous studies, the use of surfactant-based hand washing ranged from 32%, among a mix of international pilgrims who attended two hospitals in Mina in 2007, to 90% among domestic Saudi Arabian pilgrims hailing from the central region of the country who participated in the Hajj 2010.[30] The efficacy of hand washing among Hajj pilgrims in vRTI prevention should be evaluated in a future trial.

Conclusions

This cRCT shows allocation to facemask use did not protect against clinical or laboratory-confirmed viral respiratory infections. Although this cRCT could be repeated with more resourcing to improve protocol compliance, it has shown that face mask use is not an effective public health interventions to prevent vRTIs at MGs. There is a strong evidence base for the effectiveness of vaccination aginst influenza and, as reported, hand washing, as part of the Hajj rituals, was frequent. A future study should assess the role of hand hygiene either in combination with facemask use or independently as a cost-effective intervention at MGs and also explore the reasons for poor compliance with protocol.

Contributors

HR, RB, EAH, LH, DED, HEB, ECH and OB conceived the idea, designed the trial and applied for funding; MA, OB, MT, A-MB, HB, MIA, HR, GK, and members of Hajj Research Team collected data. A-MB, OB, MT, MIA and MA collated and entered the data. JK, DED, JT conducted nucleic acid testing. EHB supervised statistical analysis; MA prepared the figures and tables. RB, HEB and OB are ethics contact persons respectively in Australia, Qatar and Saudi Arabia. MA, OB, HR, LH, JT, A-MB , HEB and GJW coordinated logistics. HR is the guarantor of the study. MA, HR and EAH wrote the first draft of the manuscript; all other authors revised the manuscript. All authors approved the final version of the manuscript.

Declaration of interests

Professor Robert Booy has received funding from Baxter, CSL, GSK, Merck, Novartis, Pfizer, Roche, Romark and Sanofi Pasteur for conducting this research, travel to conferences or consultancy work; all funding received is directed to research accounts at The Children's Hospital at Westmead. Dr Harunor Rashid has received fees from Pfizer, Sanofi Pasteur and Novartis for consulting or serving on an advisory board. The other authors have no competing interests to declare.

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***Panel*: Research in context**

Evidence before this study

The evidence for the effectiveness of mask use against viral respiratory tract infections (vRTIs) from the relevant literature for randomised controlled trials (RCTs) was previously inconsistent or inconclusive. Six RCTs compared 'plain surgical facemask' with 'no intervention' against influenza-like illness (ILI) and five of these also assessed their effectiveness against vRTIs. Synthesised data from these studies indicated that using surgical facemasks had an effect on ILI but not on laboratory-confirmed vRTIs. Small sample size of individual RCTs limited their findings.

Added value of this study

This cRCT, using a large sample, investigates the realistic population use of facemasks in preventing respiratory tract infections. Its methodology is openly described and compared the offer and use of facemasks versus no facemasks among Hajj pilgrims from Saudi Arabia, Qatar and Australia in 2013, 2014 and 2015. Cluster-randomisation was done by accommodation tents. Pilgrims in intervention tents were provided with 50 free facemasks to be used for at least 5 days and they were followed regularly by trained researchers assigned to specific tents. Respiratory symptoms and facemask use were recorded daily in each participant's health diary, and nasal/pharyngeal swabs were collected from the symptomatic for real-time, multiplex PCR testing for respiratory viruses. This trial with adequate sample size shows facemask use was not associated with reduced clinical respiratory infection in both an intention to treat and per-protocol analyses.

Implications of all the available evidence

Facemasks are not effective in preventing viral respiratory infections among Hajj pilgrims. They were no a popular measure with most study participants reluctant to use them. Vaccination should be encouraged as an effectiveintervention and other barrier methods such as hand washing should be investigated in a future study.

***Table 1*: Baseline characteristics of participants across the study arms**

	Facemask n (%)	Control n (%)
Tents		
Total tents recruited	149	169
Male tent	71 (48)	72 (43)
Countries		
Gulf	137 (92)	151 (89)
Australia	12 (8)	18 (11)
Year		
2013	26 (18)	22 (13)
2014	46 (31)	55 (33)
2015	77 (52)	92 (54)
Participants		
Total participants	3,864	3,823
Participation rate	68%	69%
Average participation rate per tent	66%	68%
Gulf	3,575 (93)	3,423 (90)
Australia	289 (8)	400 (11)
2013	551 (14)	474 (12)
2014	1,106 (29)	1,128 (30)
2015	2,207 (57)	2,221 (58)
Male	1,891 (49)	1,651 (43)
Mean (SD) age y	36·9 (12·1)	37·2 (12·5)
Median (range) age y	34 (18–95)	35 (18–95)
With any risk factor	741 (19)	715 (19)
Smoking as the single risk factor	401 (10)	355 (9)
Pregnancy	32 (2)	31 (1)
Influenza vaccine uptake	1,929 (50)	1,887 (49)
Used facemask before recruitment	1,057 (28)	924 (25)

***Table 2*: Compliance with facemask and hand hygiene across the study arms**

	Facemask N=3,864 n (%)	**Control N=3,823 n (%)**	**p value**
Daily use of facemask	954 (25)	545 (14)	**0·0008**
Intermittent use of facemask	1,842 (48)	1,333 (35)	
Not used facemask	808 (21)	1,672 (44)	
Used antiseptic/hand rub	1,818 (47)	1,720 (45)	0·07
Washed hands frequently (>2 times per day)	2670 (69)	2520 (66)	**0·009**
Washed hands rarely (1–2 times per day)	578 (15)	619 (16)	
Did not wash hands	140 (4)	178 (5)	

***Table 3*: The attack rate of viral respiratory infections during Hajj in both arms**

	Total swabs N=650 n (%)	**Facemask N=358 n (%)**	**Control N=292 n (%)**	**p value**
Positive	277 (43)	149 (42)	128 (44)	0·57
Rhinoviruses	228 (35)	121 (34)	107 (37)	0·45
Influenza viruses	30 (5)	17 (5)	13 (5)	0·86
Influenza A	29 (5)	17 (5)	12 (4)	0·70
Influenza A/H1N1	9 (1)	5 (1)	4 (1)	0·98
Influenza A/H3N2	14 (2)	9 (3)	5 (2)	0·48
Influenza B	1 (0·2)	0 (0·0)	1 (0·3)	0·27
Enteroviruses	10 (2)	5 (1)	5 (2)	0·75
Parainfluenzavirus 1	5 (0·8)	3 (0·8)	2 (0·7)	0·82
Parainfluenzavirus 2	1 (0·2)	0 (0·0)	1 (0·3)	0·27
Parainfluenzavirus 3	5 (0·8)	3 (0·8)	2 (0·7)	0·82
hMPV	2 (0·3)	2 (0·6)	0 (0·0)	0·20
Human coronaviruses	3 (0·5)	2 (0·6)	1 (0·3)	0·69
Adenoviruses	3 (0·5)	1 (0·3)	2 (0·7)	0·45
RSV	2 (0·3)	2 (0·6)	0 (0·0)	0·20
MERS-CoV	0 (0·0)	0 (0·0)	0 (0·0)	-
Dual infection	13 (2)	8 (2)	5 (2)	0·64

hMPV= Human metapneumovirus.

***Table 4*: Primary and subgroup analyses by intention to treat**

	Facemask n/N (%)	**Control n/N (%)**	**OR (95% CI)**	**Sub-group p value**	**Interaction p value**
Lab-confirmed vRTIs	96/218 (44)	60/161 (37)	1·35 (0·88–2·07)	0·18	-
Influenza vaccinated	44/106 (42)	37/102 (36)	1·3 (0·7–2·2)	-	0·85
Not vaccinated	54/95 (47)	21/53 (40)	1·3 (0·7–2·2)		
At higher risk	20/42 (48)	12/31 (39)	3 (1·9–4·9)	-	0·71
Not at higher risk	71/164 (43)	45/114 (40)	1·2 (0·7–2·1)		
Smokers	11/28 (39)	5/9 (56)	0·5 (0·1–2·8)	-	0·33
Not smokers	80/179 (45)	53/138 (38)	1·3 (0·8–2)		
Male	45/101 (45)	28/50 (56)	0·7 (0·3–1·4)	0·31	**0·02**
Female	51/117 (44)	32/111 (29)	1·9 (1·2–3)	**0·004**	
Gulf	15/35 (43)	17/48 (35)	1·4 (0·6–3·4)	-	0·96
Australia	81/183 (44)	43/113/ (38)	1·3 (0·8–2·2)		
CRI	354/3,199 (11)	322/3,139 (10)	1·1 (0·88–1·39)	0·40	-

Influenza vaccinated	160/1,677 (10)	181/1,631 (11)	0·8 (0·7–1·1)	0·18	**0·004**
Not vaccinated	176/1,361 (13)	131/1,381 (10)	1·4 (1–2)	**0·03**	
At higher risk	86/621 (14)	69/615 (11)	1·3 (0·9–1·8)	-	0·28
Not at higher risk	254/2,439 (10)	239/2,399 (10)	1·1 (0·8 – 1·4)		
Smokers	40/350 (11)	30/311 (10)	1·2 (0·7–2)	-	0·86
Non-smokers	303/2,721 (11)	279/2,725 (10)	1·1 (0·8–1·4)		
Male	148/1,576 (9)	120/1,354 (9)	1·1 (0·8–1·5)	-	0·73
Female	206/1,623 (13)	202/1,785 (11)	1·2 (0·9–1·6)		
Gulf	332/3,043 (11)	287/2,954 (10)	1·2 (0·9–1·5)	-	0·13
Australia	22/156 (14)	35/185 (19)	0·7 (0·4–1·3)		

CRI=Clinical respiratory infection. vRTIs=viral respiratory tract infections.

***Table 5*: Per protocol analysis: effect of facemasks against laboratory-confirmed viral respiratory tract infections**

vRTIs based on facemask use		**Facemask**	**Control**	**OR* (95% CI; p value)**
Did not use facemask				1·21 (0·87 to 1·69; 0·26)
Laboratory results	Positive	29 (45)	50 (41)	
	Negative	35 (55)	72 (59)	
Used facemask daily				
Laboratory results	Positive	46 (50)	20 (53)	
	Negative	47 (50)	18 (47)	

*Analysis includes only participants allocated to facemask who used facemasks daily (n=93) and those allocated to Control who did not use facemasks (n=122).

***Table 6*: Per protocol analysis: effect of facemask against CRI**

CRI based on facemask use		**Facemask**	**Control**	**OR* (95% CI; p value)**
Did not use facemask				1·3 (0·99 to 1·83; 0·06)
CRI	Yes	55 (8)	141 (9)	
	No	648 (92)	1356 (91)	
Used facemask daily				
CRI	Yes	97 (12)	38 (8)	
	No	731 (88)	425 (92)	

*Analysis includes only participants from Facemask group who used facemasks daily (n=828) and those from Control group who did not use facemasks (n=1497).

***Figure 1*: Trial profile**

***Figure 2*: Prevalence of clinical respiratory infection by compliance to facemask use in individual tents**

***Figure 3*: Reasons for not using facemasks across the study arms**

Figure 1

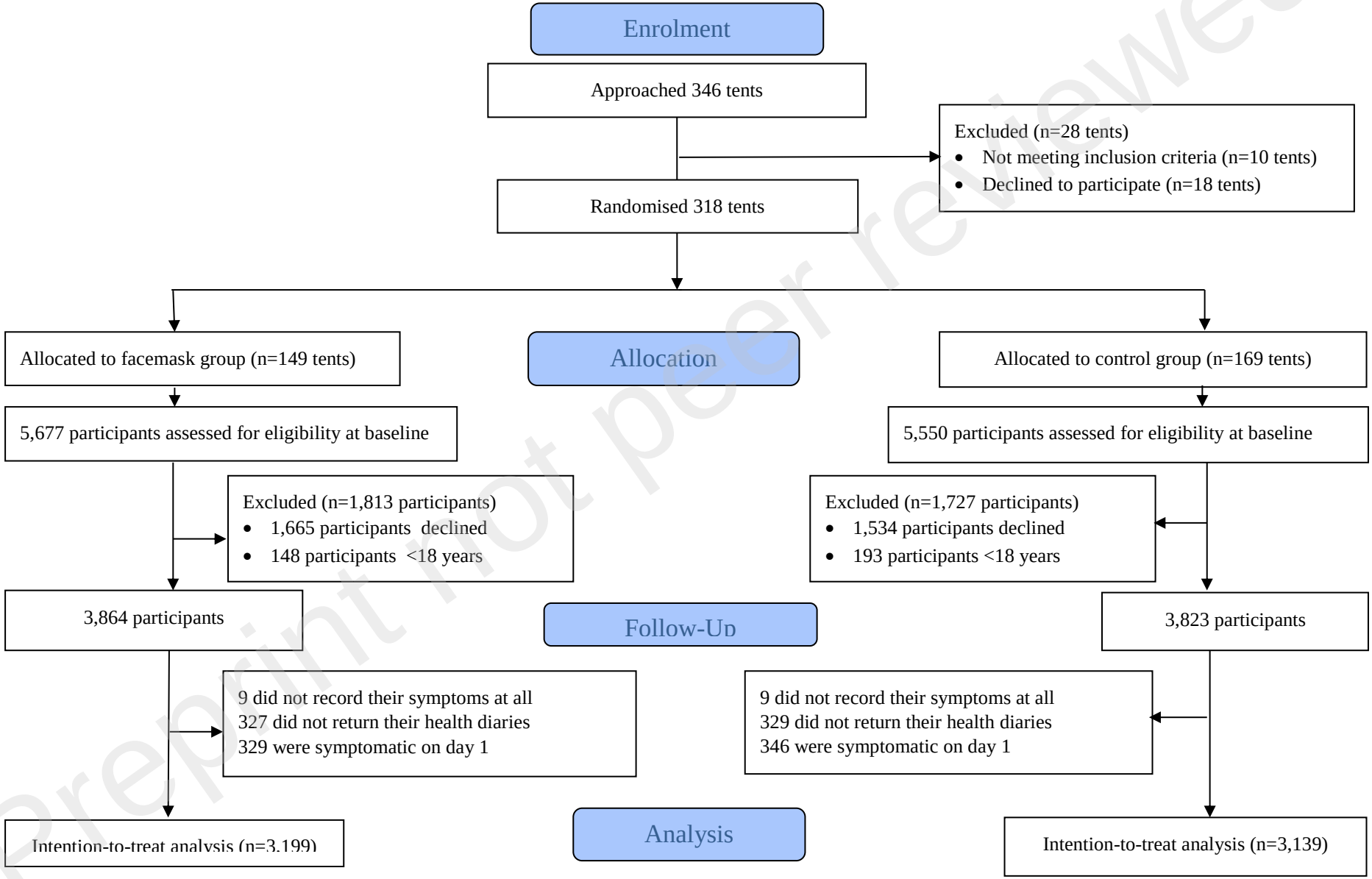


Figure 2

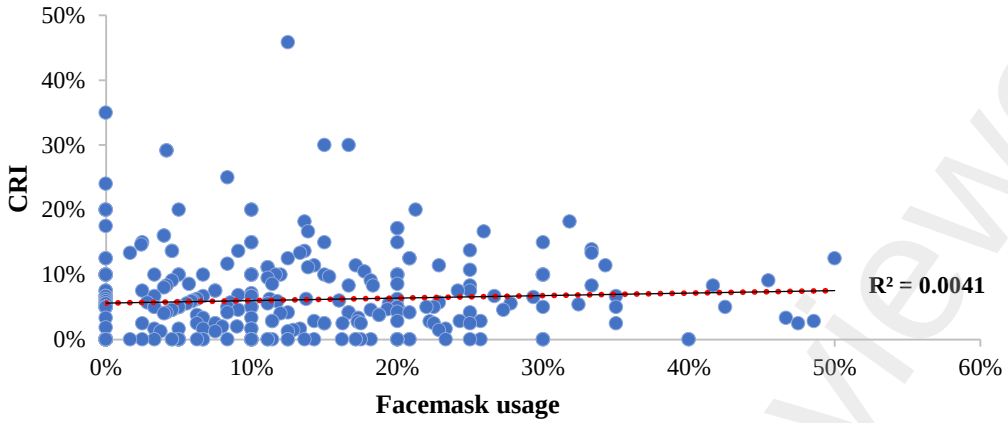
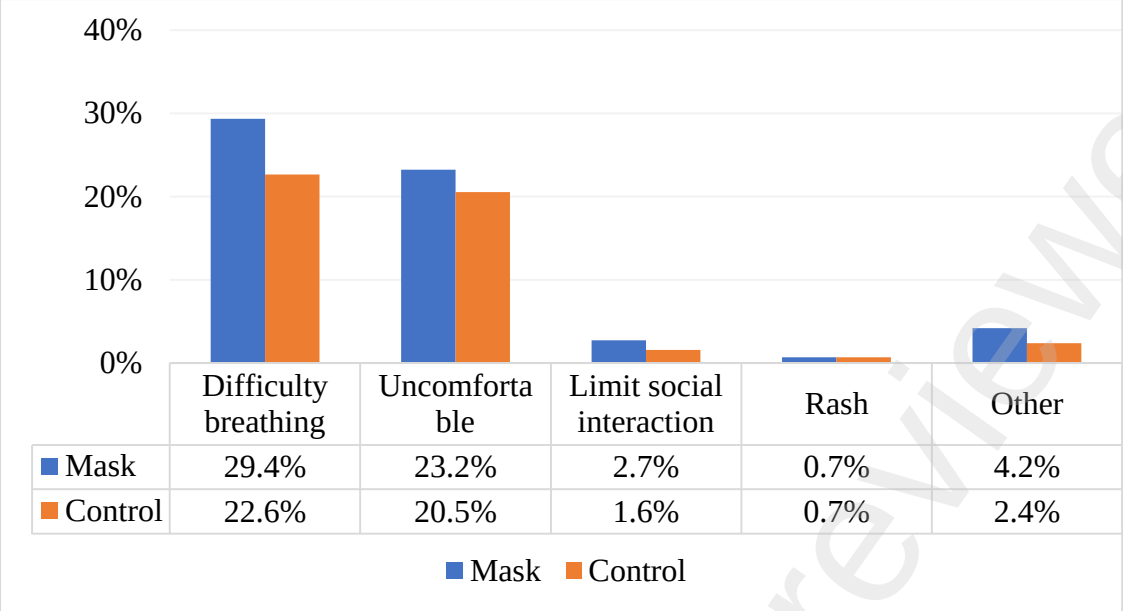


Figure 3



	Difficulty breathing	Uncomfortable	Limit social interaction	Rash	Other
Mask	29.4%	23.2%	2.7%	0.7%	4.2%
Control	22.6%	20.5%	1.6%	0.7%	2.4%

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Mohammed Al-Fageeh, Mohammed Alaamri, Mohammed Al-Jeddawi, Mohammed Alshreef, Mohammed Alsaggaf, Mohammed Dumyati, Mohammed Al- Mikhlafi, Mohsen Alzamanan, Mona Alghamdi, Muhab Hindi, Muteb Almarwani, Nada Telmesani, Nada Mohammed, Naif Alhowaiti, Nasser Alshehri, Nedaa Karami, Neveen Awad, Nizar Almaghrabi, Nojoud Hli, Nuha Jazzar, Omar Alzhrani, Omar Alotaibi, Osama Alharbi, Qutaibah Aldurrah, Raghad Namnqani, Rahma Al-Ghamdi, Raid Alghamdi, Rana Almimoni, Rana Abbas, Raneem Rawa, Rayyan Alqurayyan, Razan Melibari, Reem Altaifi, Reem Bajunaid, Reem Altowairqi, Reem Alenazi, Reem Alghamdi, Refal Aziz Al-Rahman, Reham Bin Hassan, Roaa Khan, Rowaynah Aziz Al-Rahman, Ruba Alshaikh, Saad Algarni, Saadiah Balkhy, Saeed Balubaid, Safa'A Al-Hasani, Sahar Futtiny, Salman Melhem, Salwa Alotaibi, Samah Alqurashi, Samaher Melybari, Sana Nargis, Sara Alshehtha, Sarah Radwan, Saud Bakhsh, Shahad Bamani, Shahad Alharbi, Shahd Hafiz, Shoroug Alkhabiry, Sofana Alqawsi, Sultan Alzahrani, Sultan Shaqra, Thamer Alanazi, Wafa Alkhuzaie, Wafa Sidiqqi, Wafaa Altaezi, Wafaa Alharbi, Walid Almutairi, Wasaif Aljuhany, Wed Jawa, Yaser Badawood, Yasser Hadi, Yousef Alzahrani, Abaad Al-Mutairi, Abdulaziz Ajaj, Abdullah Tai, Abdullah Ashour, Abdullah Aljohni, Abdullah Alshehri, Abdullateef Allebdi, Abdullateef Alzhrani, Abdulmajeed Alzahrani, Abrar Alnami, Adel Almaymuni, Afnan Joudah, Ali Fadel, Ali Alshehri, Ali Alelyani, Ali Alkhulaifi, Amal Alnakhli, Amani Alharbi, Anas Heji, Arwa Badakhan, Asal Arbaeen, Asmaa Nassir, Basim Almutairi, Atrab Bayazeed, Bushra Alahmadi, Dania Almunami. Dareen Alsaidalany, Ebtehal Yamani, Ebtesam Alghamdi, Eman Alharbi, Eman Kotbi, Fahad Altowairqi, Faisal Althobaiti, Faisal Alsobyani, Farraj Al-Zahrani, Ghadah Althbiti, Ghadah Alshehri, Hadeel Alqahtani, Hanan Mughallis, Haneen Taher, Heba Bayoumi, Hesham Essa, Hussein Alshamrani, Khalil Alghamdi, Malak Alshammari, Maram Albarakati, Marwah Bin-Garhom, Marwan Albeshri, Mohamed Bayoumi, Mohammad Althobaiti, Mohammed Toras, Mohammed Al Thebyani, Naif Alzahrani, Nasheal Bawahhab, Noura Al-Zahrani, Ohoud Alharbi, Radwan Badr, Rahma Aljedaani, Rakan Alnefaie, Rawa'A Al-Maghrabi, Rehab Alshamrani, Reham Abdulgader, Riyadh Alharbi, Sara Al-Ghfari, Sarah Aljoudi, Saud Alzhrani, Somayah Alsolami, Suliman Badi, Sultan Alghamdi, Tawfiq Al Laylah, Wasfi Almusaddi, Wijdan Alzhrani.

*Protocol

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A cluster-randomised controlled trial to test the efficacy of facemasks in preventing respiratory viral infection among Hajj pilgrims

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KEYWORDS

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Abstract *Background:* Cost-effective interventions are needed to control the transmission of viral respiratory tract infections (RTIs) in mass gatherings. Facemasks are a promising preventive measure, however, previous studies on the efficacy of facemasks have been inconclusive. This study proposes a large-scale

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Middle East respiratory syndrome coronavirus; Viral respiratory tract infection

facemask trial during the Hajj pilgrimage in Saudi Arabia and presents this protocol to illustrate its feasibility and to promote both collaboration with other research groups and additional relevant studies.

Methods/design: A cluster-randomised controlled trial is being conducted to test the efficacy of standard facemasks in preventing symptomatic and proven viral RTIs among pilgrims during the Hajj season in Mina, Mecca, Saudi Arabia. The trial will compare the 'supervised use of facemasks' versus 'standard measures' among pilgrims over several Hajj seasons. Cluster-randomisation will be done by accommodation tents with a 1:1 ratio. For the intervention tents, free facemasks will be provided to be worn consistently for 7 days. Data on flu-like symptoms and mask use will be recorded in diaries. Nasal samples will be collected from symptomatic recruits and tested for nucleic acid of respiratory viruses. Data obtained from questionnaires, diaries and laboratory tests will be analysed to examine whether mask use significantly reduces the frequency of laboratory-confirmed respiratory viral infection and syndromic RTI as primary outcomes.

Conclusions: This trial will provide valuable evidence on the efficacy of standard facemask use in preventing viral respiratory tract infections at mass gatherings.

This study is registered at the Australian New Zealand Clinical Trials Registry (ANZCTR), ACTRN: ACTRN12613001018707 (http://www.anzctr.org.au).

1. Introduction

Viral respiratory tract infections (RTIs), including influenza, are a major burden to public health. During any inter-pandemic year, there are an estimated 1 billion cases of influenza worldwide with 3—5 million cases of severe illness and 300,000—500,000 deaths [1]. Fear of the global spread of serious respiratory disease persists in the light of past pandemics, such as the severe acute respiratory syndrome (SARS), the influenza A (H1N1) pdm09 virus, and the recent emergence of the Middle East respiratory syndrome coronavirus (MERS-CoV) [2]. Ever-increasing international travel intensifies the risk of the spread of emerging novel viruses, further intensifying the concern [3]. Mass gatherings such as the Hajj pilgrimage pose a particular risk for transmission of respiratory viruses [4,5].

Health authorities require cost-effective measures that prevent or limit the global transmission of respiratory diseases. Facemasks represent a simple and cheap supplement to the use of handwashing, antivirals, and vaccination in the control of viral RTIs.

Results from previous studies examining the effectiveness of facemasks have been either conflicting or inconclusive [6—17]. A randomised controlled trial (RCT) in a household setting found that adherence to facemask use decreased the risk of influenza-like illness (ILI) [7]. Meta-analysis of data from 6 trials shows that wearing facemasks is protective against ILI, but did not show that facemasks are protective against laboratory-confirmed influenza, perhaps due to limitations of the studies (Fig. 1) [18]. Interestingly, one nested case—control study showed that intermittent facemask use was associated with a significantly greater risk of infection among healthcare workers at Hajj, suggesting perhaps that infectious material that settles on facemasks can become a source of direct hand transmission to the respiratory tract [19]. Standard facemasks may prevent: (i) acquisition of infection by droplet and/or aerosol spread, or conversely, (ii) transmission from infected subjects [20,21].

The major limitation of previous studies is their small sample size, and resulting lack of study strength to detect important, albeit moderate (e.g. 40—50%), protective effects of facemasks on laboratory-confirmed influenza or other infections [6,18]. The largest study undertaken to date was a cluster-randomised trial in 509 households, with 2788 recruits; it did not find an additional benefit from the combination of facemasks and hand hygiene over health education (regarding preventive measures) on the overall rate of laboratory-confirmed viral infection, although there was a benefit against secondary transmission of RTI and laboratory-confirmed influenza. The authors pointed to concerns about both under-powering of the study and poor compliance with mask use [11]. Bin Reza et al. recommended that sufficient power may be achieved by larger trials that are multi-centred and run for several years [6]. The authors of this study contend, in addition, that

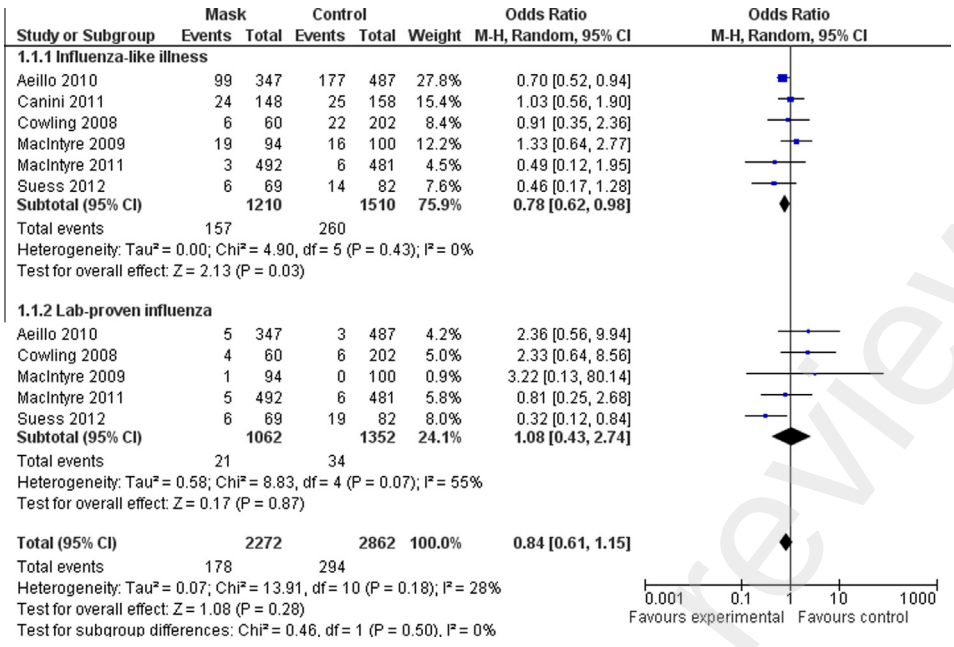

Fig. 1 Comparison between mask and control groups in randomised trials (adapted from Rashid et al. with the inclusion of an additional study [9,18]).

taking important steps to improve compliance with mask use is also critical to inducing a form of herd immunity through widespread mask use. There are considerable logistic and cost issues to consider in the design and conduct of such trials, but the public health benefits of a positive result could be substantial.

Conducting a trial during the Hajj pilgrimage, where approximately 2—3 million people gather annually from all corners of the world and stay for at least 4 days in tents in the Mina valley, offers an excellent opportunity to conduct research in a semi-closed setting.

This study aims to evaluate the efficacy of facemasks in preventing laboratory-confirmed respiratory viral infections and syndromic RTIs. Concurrently, the transmission pattern of influenza at Hajj will be investigated by studying the genetic relatedness between circulating strains using deep genomic sequencing. In addition, the uptake of influenza will be determined and its effectiveness at Hajj will be evaluated using a test-negative case—control design.

2. Methods

2.1. Primary end point

- To evaluate the efficacy of facemasks against laboratory-confirmed respiratory viral infections (including influenza, MERS CoV and other respiratory viruses) at Hajj.

2.2. Secondary end points

- To investigate the transmission pattern of the influenza virus at Hajj by studying the genetic relatedness between circulating influenza viruses using deep genomic sequencing.
- To determine the self-reported influenza vaccine uptake and evaluate its effectiveness at Hajj using a test-negative case—control design.

2.3. Study design

A large-scale cluster-randomised controlled trial has been planned to compare the 'supervised use of facemasks' versus 'standard measures' (where some may choose to use a facemask) among pilgrims during three consecutive Hajj pilgrimages. Cluster-randomisation to each arm will be in a 1:1 ratio and will be done according to accommodation tents. Computer-generated random numbers will be generated by an offsite research coordinator who will not take part in the recruitment or assessment of participants. The randomisation will be stratified by gender and country of residence to ensure a balanced and proportionate recruitment. The key steps of the study are shown in Fig. 2.

2.4. Recruitment

At the 2013 Hajj, over 1000 pilgrims were recruited from Saudi Arabia, Qatar and Australia, whereas in

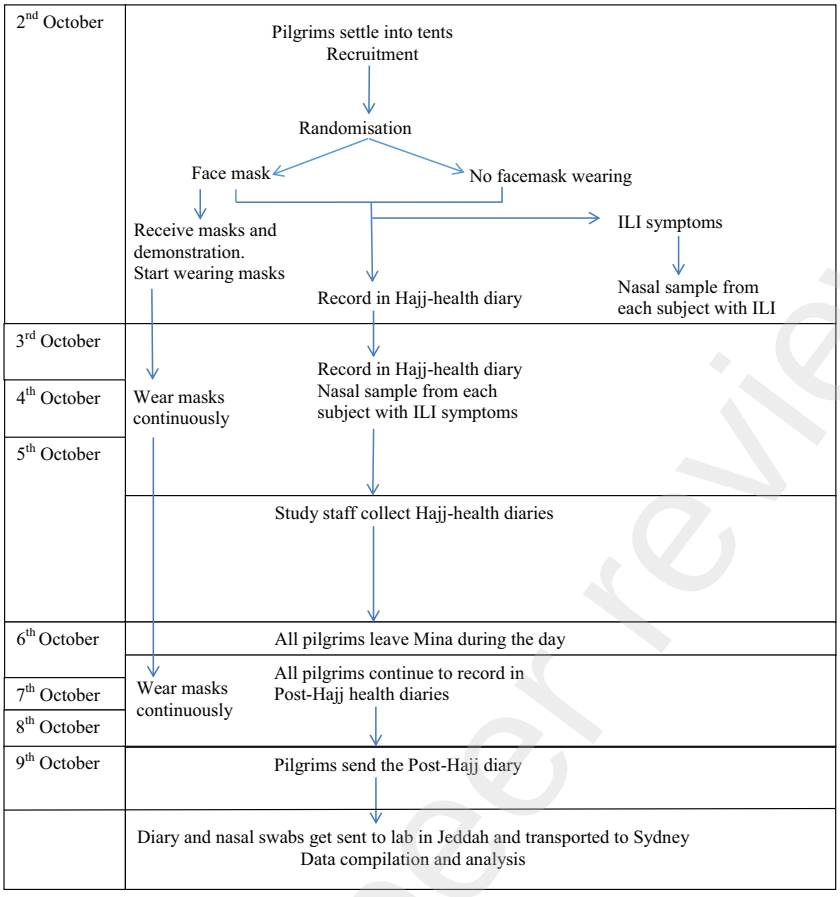

Fig. 2 Key steps of the study at the Hajj 2014 (these key steps will remain the same in 2015 except that the recruitment dates will advance by 11 days).

Table 1 Proposed number of pilgrims from each participating country.

Countries	Total number of pilgrims	Number of recruits	
		2013	2014
Saudi Arabia	1,000,000	2,200	2200
Indonesia	200,000	—	500
India	170,000	—	450
Pakistan	150,000	—	350
Turkey	120,000	—	300
Bangladesh	65,000	—	200
Morocco	32,000	—	100
Malaysia	28,000	—	100
Australia	5000	200	200
Qatar	2000	100	100
Total	1,770,000	2500	4500

2014/2015, participants will also be recruited from at least some of the following countries: Indonesia, Malaysia, Turkey, Morocco, India, Pakistan and Bangladesh (Table 1).

Before the commencement of Hajj, all tour groups will be provided with detailed information about the study while in their own country and encouraged to participate. At Hajj, trained study staff will approach tour group leaders in each tent for recruitment on the first day of the pilgrims' stay in Mina. The research team members will explain the study in detail to the assembled pilgrims and invite them to participate in the study. If they agree, informed consent will be obtained and a baseline questionnaire will be completed which will include data on demographics and clinical information, such as recent respiratory symptoms (Appendix A). Participants and caregivers will not be blinded to the randomisation and will be informed about their allocation (supervised face-mask wearing or standard care); however, laboratory staff and statistical analysts will be blinded to the allocation.

2.5. Inclusion and exclusion criteria

2.5.1. Inclusion

- Pilgrims from participating countries staying in their respective tents.
- Age $\geqslant$ 18 years.
- The participant should be able to provide signed informed consent.

2.5.2. Exclusion

- Age < 18 years.
- Participation in another clinical trial investigating a medical intervention that may interfere with the study outcome measures, like laboratory-confirmed viral RTI.
- Any known contraindication to mask use (e.g., allergy to standard [surgical] mask materials).
- Refusal/or inability to sign the consent form.

2.6. Data collection

For the tents assigned to mask use, 30 facemasks will be provided to each participant, to be worn continuously (24/7 if possible), and replaced every six hours (sooner if wet), for use during the 4 days at Mina, including Arafat, and preferably for the additional 3 days after leaving Mina.

The standard facemask for this study is '3M™ Standard Tie-On Surgical Mask, Cat No: 1816'. Masks may be briefly removed for eating, praying, washing, brushing teeth, or if the pilgrim experiences discomfort. Oral and written information about the instructions for correct mask wearing and disposal will be provided to the mask group (Appendix B). Study staff will practically demonstrate the correct method of how to wear a mask and also help pilgrims put on their masks for the first time. Small plastic bags will be provided for mask disposal and subjects will be instructed to discard the plastic bag containing used masks into local waste bins. A subset of used masks will be saved for further testing by multiplex viral PCR.

A research team member will visit tents each morning and evening to distribute additional facemasks should pilgrims require extra, and to document the development of any reported RTI symptoms.

Study staff will *inter alia* record each tent number, the number of people recruited, and the total number of people in each tent. Pilgrims will be provided with a *Hajj Health* diary (Appendix C) for the 4 days at Mina (corresponding to 2014 with 2—5 October) and a second diary, hitherto named *post-Hajj Health* diary (Appendix D), for the next 3 days after leaving Mina. Each diary will have a unique identifying barcode linked to the study participant number. The diaries (Appendices C and D) will contain questions on demographics, medical conditions, and influenza vaccination history. Each participant, whether in an intervention or a control tent, will provide information about the presence or absence of respiratory symptoms and fever in the diary every day, whenever it is most convenient (morning or evening). Pilgrims will also record in their diaries the amount of time they have worn the mask, the number of masks used that day and whether they were wearing one during their sleep overnight. In addition to English, the study documents (diaries and questionnaires) will be available in various languages, including Arabic, Bahasa Indonesia and Bahasa Malaysia, and the multilingual research team members will remain available to help the participants who do not speak English.

Masks will not be provided to anyone in the control tents, although pilgrims may use their own supply of masks.

The *Hajj Health* diary (Appendix C) will be collected on the evening of the fourth day. At the same time, the *post-Hajj Health* diary (Appendix D) will be distributed to these pilgrims with self-addressed prepaid envelopes. Pilgrims will be instructed to post these diaries to the researchers or tour operators may collect them on behalf of the study. Pilgrims whose *Hajj Health* diaries (Appendix C) were not collected on the fourth day will be instructed to return them together with their *post-Hajj Health* diaries (Appendix D) in the same envelope.

2.7. Specimen collection and testing

In both groups, the study staff will actively search for pilgrims suffering from RTI (defined as subjective or measured fever and at least one respiratory symptom such as cough, sore throat and rhinorrhoea) twice a day. A nasopharyngeal (NP) swab (or throat swab if an NP swab is too difficult to obtain) will be collected from symptomatic pilgrims by a trained staff member for later molecular diagnostic testing to detect respiratory viruses. The swab used will be a Copan Nylon® Flocked nasal swab in a viral transport medium.

As a part of the routine care, pilgrims in both groups will be supplied with generic medications (such as acetaminophen and ibuprofen) for fever or aches.

The swabs will be stored within 2—3 h of collection at −20 °C and later shipped for molecular diagnostic testing at the Centre for Infectious Diseases and Microbiology Laboratory Services (CIDMLS), Westmead Hospital, NSW, Australia. Pilgrims will be asked to provide their email address, phone number and mail address if they wish to receive the result of the laboratory test. Nucleic acid testing using a multiplex reverse transcriptase polymerase chain reaction (RT-PCR) for influenza A and B, MERS-CoV and other coronaviruses, parainfluenza viruses (types 1, 2, 3 and 4), RSV A and B,

adenoviruses, human metapneumovirus (hMPV), and picornaviruses will be performed on nasal swabs.

2.8. Transmission dynamics

To determine the transmission patterns of influenza viruses among Hajj pilgrims, complete genome sequence of influenza viruses will be obtained using a next-generation deep sequencing protocol — using the Illumina MiSeq sequencer available at the Westmead Hospital — which will generate multiple reads per host (~1000× coverage per host). All sequence data generated will be assembled and aligned using the Geneious (http://www.geneious.com) and VICUNA packages [22], with downstream phylogenetic (and other evolutionary) analysis undertaken using the Geneious, Seminator [23], PhyML [24] and BEAST packages [25]. With these data in hand, it will be possible to investigate: (i) whether the study participants were infected prior to or during the Hajj, (ii) whether there was direct viral transmission among the study participants (such that they harbour very closely related 'majority' and 'minority' genetic variants), and (iii) if direct transmission is established, whether this occurs more frequently in the mask versus control groups.

Respiratory samples will be stored for 2 years to revalidate any results, and then discarded according to the standard operating procedure of CIDMLS.

2.9. Follow up

All participants will be followed up (e.g. by telephone, mail, email) in their country of residence to collect their *post-Hajj Health* diaries (as well as *Hajj Health* diaries if not collected earlier). Consent to study participation allows for the contact of GPs/family physicians (if available) to validate any clinical detail, including vaccination history and subsequent infection, GP consultation, or hospital admission.

2.10. Data analysis

Data available from questionnaires, diaries and laboratory tests will be analysed anonymously to examine whether mask use makes a significant difference in reducing the frequency of laboratory-confirmed respiratory viral infection (including influenza, coronavirus or other respiratory viruses) or syndromic RTI. The primary endpoints (efficacy of facemasks against RTI and laboratory-confirmed viruses respectively) will be analysed by intention-to-treat.

The self-reported uptake rates of influenza vaccination will be determined and vaccine effectiveness will be estimated based on the case-negative case—control methodology.

The results from the genomic sequencing of the influenza virus will assist us in understanding the genetic relatedness of circulating influenza strains at Hajj and the transmission pattern of influenza among pilgrims.

2.11. Sample size calculation

Assuming a moderate intra-cluster correlation of 10% and a mean of 75 participants per cluster (tent), and inflating the sample by a moderately large factor of 8.4 to account for clustering, the sample size required for a cluster-randomised controlled trial to detect a reduction in laboratory-confirmed viral respiratory infection from 12% to 6% with 80% power at 5% significance is 2976 per arm. An additional inflation factor of 1.18 will allow for up to a 15% loss to follow-up, loss due to *a priori* infection with high penetration or incomplete outcome data. These results in a sample size of approximately 3500 participants per treatment making a total of 7000.

For the first primary outcome (clinical/syndromic RTIs) a smaller sample would be sufficient to answer a more generic question, namely prevention of symptomatic RTI. The sample size required for detecting a reduction from 30% prevalence of RTIs to 15% with 80% power at 5% significance and adjusting for clustering and loss of follow-up is about 1170 participants per treatment making a total of 2340 [26,27].

To achieve the full sample size, the aim will be to conduct the study over three years. It will be attempted to recruit a proportionate (or balanced) number of pilgrims from each participating country according to the number of pilgrims attending Hajj from these countries (see Table 1).

2.12. Ethical implication

The trial has received approval from an Australian Human Research Ethics Committee (NSW HREC Ref: HREC/13/HNE/265), and the Joint Institutional Review Board (J-IRB) of Hamad Medical Corporation - Weill Cornell Medical College in Qatar (IRB Number: 13-00039). The study coordinators of each participating country will provide a modified Ethics Committee submission for collaborators and assist them in applying for ethical approval from the relevant Committees. Only participants who provide written informed consent to take part will be included in this study. Participants will be

told that taking part in this study would be voluntary and confidential. All participants will be assigned a study identification (ID) number. Data will be collected and stored under this number only, so that all data are stored anonymously using study ID number. Hard copies of the questionnaires will be stored securely in a locked filing cabinet in locked offices and electronic data will be stored in password-protected computer files. Only members of the research team will have access to the data. The hard copies will be retained for at least 15 years (or more, if the data management protocol of the participating country requires so) and will be disposed according to standard data management guidelines.

3. Discussion

If conducted successfully, this study will be the largest trial assessing the efficacy of standard facemasks against RTIs (including influenza), and thus would add to the evidence compendium on physical interventions for response to an influenza pandemic. In addition, this will be one of the largest studies to be conducted at Hajj involving extensive international collaboration. Additionally, this study will address the newly emerged MERS-CoV threat and the potential role of facemasks in its prevention. It is also hoped to involve international collaborators in studying the burden of nasopharyngeal acquisition of antibiotic-resistant colonising microbes, and assessing the impact of facemask use on the prevention of such infections.

However, there are many challenges. An efficient orchestration of the trial is needed to achieve the study objectives; this include training a large number of study research volunteers ($n = 500$), leading the team to conduct the trial, appropriate data collection, and storage and transport of samples in optimum temperature. Additionally, the compliance with facemask use in intervention tents must be optimised. Some ''contamination'' may occur whereby subjects in control tents may use facemasks. These issues would be addressed by analysing data with respect to compliance of facemask use, in addition to intention-to-treat analysis. Study staff will visit the intervention tents twice a day to encourage mask use and advise people if they have problems with wearing facemasks. Study staff will similarly visit the control tents and encourage the recruits to strictly maintain a record of any facemask use, to complete their diary and to collect samples from symptomatic pilgrims. A recent pilot study showed that high compliance could be achieved, up to 76%, where facemask usage was recommended and the purpose explained [28].

The MERS-CoV threat may impact this study in another way. While it highlights the significance of this trial in investigating respiratory diseases at Hajj, the Saudi Arabian Ministry of Health has recommended that those at high risk of MERS infection (e.g. those with chronic medical conditions, pregnant or aged 65+ years) postpone their pilgrimage and that those who perform Hajj use facemasks in crowded places and amongst coughing pilgrims [29]. This means that the confounding behaviour of controls will be carefully measured and included in multiple regression analysis.

All diaries may not be returned despite the sincerest of efforts. Pilgrims are required to post the second set of diaries (*post-Hajj Health* diaries) in reply-paid self-addressed envelopes, which they might not do on time. To optimise the return of the diaries, their study coordinators in respective countries will send phone/mail reminders to the recruits, and tour operators will assist in diary collection.

Data quality may not be optimum as it relies on self-reported symptoms. Reporting of RTI symptoms may be dictated by the patient's interests: patients may report more specific symptoms to their physicians to get a prescription for antipyretics/pain killers. Study staff will frequently monitor this, but continuous monitoring will not be feasible.

In addition, the short follow-up duration of this trial means there is a possible failure to detect some infections. The incubation period of respiratory viruses may range from less than 2 days (e.g., rhinovirus and influenza) to more than 5 days (adenovirus, MERS-CoV) [30,31]. However, it is believed that *post-Hajj Health* diaries will reduce this shortcoming to some extent.

Despite these limitations, if successful, this project will provide valuable data on the efficacy of simple facemasks in preventing viral respiratory infection in Hajj pilgrims. It is believed that this data may be useful to other mass gatherings, such as the Olympics, and perhaps to other closed settings such as hospitals, schools, airplanes, ships and airport settings. It also represents a powerful opportunity to study precise patterns of virus transmission through detailed comparison of circulating viral strains. It is hoped that the outcomes of this study will inform global health authorities about the effective control of respiratory viral infection.

Conflict of interest

Professor Robert Booy and Dr. Leon Heron have received funding from Baxter, CSL, GSK, Merck, Novartis, Pfizer, Roche, Romark and Sanofi Pasteur

for the conduct of sponsored research, travel to present at conferences or consultancy work; all funding received are directed to research accounts at The Children's Hospital at Westmead. Dr. Iman Ridda has received Grants for investigator-driven research from GSK and for consultation from Merck. The other authors have declared no conflict of interest in relation to this work.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jegh.2014.08.002.

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